The Use of Doppler Flow Velocity Measurement to Assess the Hemodynamic Response to Vasodilators in Patients with Heart Failure

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SUMMARY To determine if the hemodynamic response to vasodilator therapy can be assessed noninvasively by pulsed Doppler velocimetry, we compared the hemodynamic changes after treatment to changes in Doppler aortic blood flow measurements. The relationship between the absolute values and percent changes of invasively measured systemic vascular resistance (SVR) and stroke volume (SV) and Doppler-measured peak flow velocity (PFV), left ventricular ejection time (ET) and flow velocity integral (FVI) were evaluated. Measurements were made during 18 drug interventions in 13 patients treated with vasodilator agents for congestive heart failure (CHF). A poor correlation was found between the absolute values of either SVR or SV and the absolute values of each of the three Doppler aortic blood flow indexes studied. In contrast, a good correlation was found between percent changes in aortic PFV and in SVR ($r = -0.89$), and between percent changes in Doppler aortic FVI and in SV ($r = 0.88$). The correlation between percent changes in SVR and FVI revealed an $r$ value of $-0.65$, while the correlation between percent changes in SVR and in ET showed an $r$ value of $-0.15$. Percent changes in SV and either PFV or ET correlated with $r$ values of 0.75 and 0.70, respectively. We conclude that Doppler aortic blood flow measurement can be used to assess quantitative changes in SVR and SV after vasodilator therapy. These findings suggest that it may be useful for evaluating vasodilator drug therapy in patients with CHF.

THE INDIVIDUAL RESPONSE to vasodilator therapy for congestive heart failure (CHF) has led to a common recommendation for the use of invasive hemodynamic monitoring to assess the efficacy of various drug doses.$^{1-4}$ This approach, although useful, is associated with some morbidity and increased cost of therapy. A simple and reliable noninvasive method for the assessment of the efficacy of vasodilator therapy is needed.

In this study we assessed the relationship between hemodynamic changes measured by invasive methods and changes in Doppler aortic blood flow velocity variables after vasodilator therapy and investigated the feasibility of using this information to predict the effects of therapy in patients with CHF.

Methods

Patients

Our study group consisted of 13 patients (12 men and one woman, ages 34–79 years) treated with vasodilator agents for CHF. The etiology of CHF was coronary artery disease in eight patients and dilated (congestive) cardiomyopathy in five. The diagnosis was based on cardiac catheterization in seven patients and on clinical, electrocardiographic, echocardiographic and radioisotopic criteria in six. All patients were in sinus rhythm during the study.

Eighteen drug interventions were performed: i.v. nitroprusside, 100–400 µg/min, in seven patients, oral hydralazine, 50–150 mg, in six, oral isosorbide dinitrate, 20–100 mg, in four, and a combination of oral hydralazine, 100 mg, and 2 inches of nitroglycerin ointment in one patient.

Hemodynamic Studies

Hemodynamic evaluation was performed using a Swan-Ganz thermodilution catheter (American Edwards Laboratories) inserted into the pulmonary artery. Right atrial (RAP), pulmonary arterial (PAP) and pulmonary capillary wedge (PCPW) pressures were recorded. Mean pressures were measured by using an electronic damping circuit on the bedside pressure monitor. Heart rate was determined from the bedside electrocardiographic monitor. Arterial blood pressure measurements were obtained using the standard cuff method or through an arterial cannula inserted either percutaneously or by cutdown into the radial artery. Cardiac output (CO) was determined by thermodilution using 5% dextrose in water as the indicator. CO was taken as the mean of three consecutive determinations with less than 10% variation. Computations were performed using a bedside thermodilution CO computer (American Edwards Laboratories, model 9520A).

The following calculations were made from hemodynamic data: mean arterial blood pressure (MBP) = $D + (S - D)/3$, where $S$ = peak systolic and $D$ = diastolic blood pressures; stroke volume (SV) = cardiac output/heart rate; systemic vascular resistance (SVR) = 80 [(MBP - mean RAP)/CO].

Aortic Blood Flow Studies

Doppler aortic blood flow velocity measurements were made using a spectrum analyzer–based, range-gated, pulsed Doppler velocimeter (Ultra Imager, Electronics for Medicine/Honeywell Corporation).
This instrument uses the spectral analysis approach to sample the Doppler frequency shift every 5 msec. This technique, in contrast to methods that use a zero-crossing Doppler detector, is less sensitive to noise in the Doppler signal. In the instrument used in the present study, the Doppler frequency shift of the ultrasound signals returning from the moving red blood cells are detected and converted into the corresponding flow velocity by a dual-channel spectrum analyzer. Each 5-msec sample of the Doppler signal is recorded on a strip chart with the Doppler velocity on the vertical axis versus time on the horizontal axis (fig. 1). The frequency shifts during each 5-msec sampling interval were brightness-modulated and displayed such that the velocity being traveled by the largest number of red blood cells produced the greatest darkening on the strip chart. The frequency shifts produced by smaller numbers of moving red blood cells produced progressively less darkening on the strip chart. Frequency shifts corresponding to flow velocities of less than 10 cm/sec in either direction were attenuated by high-frequency bandpass filters and displayed as a relatively white area around the zero flow velocity line (fig. 1). Flow velocity patterns and an ECG tracing were displayed in real time at a 100-mm/sec sweep speed on the oscilloscope screen and selectively frozen on the screen. The frozen image was then recorded on glossy black-on-white electrostatic paper at a paper speed of 50 mm/sec. This allowed the signals to be recorded on a strip chart at an equivalent paper speed of 100 mm/sec.

Ascending aortic blood flow was studied using a right-angled, 2.25-MHz M-mode transducer positioned in the suprasternal notch. The “mapping” technique was used to detect peak ascending aortic blood flow velocity. To perform the mapping, the Doppler instrument control was initially adjusted with the range-gated sample volume located approximately 3 cm from the transducer face. The transducer was angulated until Doppler blood flow velocity signals were obtained from the ascending aorta. Minor manipulations of the transducer were performed at that sample volume depth until maximum ascending aortic blood flow velocity was obtained. The maximum velocity was identified by listening to the audible signal from the Doppler velocimeter and by noting the peak velocity from the tracing visualized on the oscilloscope screen. The distance from the transducer to the nearest boundary of the sample volume was then changed at 1-cm intervals up to 9 cm. At each sample volume depth, a repeat attempt was made to obtain the maximal flow velocity. The flow signal used to determine the ascending aortic flow indexes was the flow signal from the sample volume depth that produced the greatest maximum blood flow velocity. An identical sample volume depth was used for the studies both before and during therapeutic interventions.

Aortic Blood Flow Data Analysis

To minimize the effect of respiration on the results, the beat displaying the greatest peak flow velocity (PFV) was selected for our analysis from a series of flow velocity recordings. The following aortic flow indexes were measured (fig. 1). Peak aortic flow velocity was measured at the midpoint of the Doppler flow spectrum at the point of maximum blood flow velocity. Ejection time (ET) was measured as the time from the onset to the end of the systolic flow velocity signal. As ET is rate-dependent, it was also corrected for heart rate using the formula of Weissler et al. The area under the aortic flow velocity curve, i.e., flow velocity integral (FVI), was calculated using the formula FVI = 1.14 (PFV × ½ ET) + 0.30. This formula was obtained by comparing the planimetered area under the flow velocity curve during systole to a mathematical approximation in 34 patients with a wide range of flow velocity integrals. The mathematical approximation of the area under the flow velocity curve was based on multiplying PFV times one-half the ET. The correlation coefficient between the estimated and the actually measured FVI was 0.97 (fig. 2).

In 14 studies, baseline hemodynamic measurements were obtained concomitantly with Doppler aortic blood flow measurements. Measurements were repeated at the expected peak effect of the given drug (1–2 hours after the administration of oral isosorbide dinitrate and oral hydralazine and 10 minutes after the initiation of intravenous nitroprusside). In four studies, the protocol was performed in reverse order as the initial study was performed during therapy and then repeated 15 minutes after discontinuation of drug administration. (Nitroprusside was the drug used in all four studies.)

Data Analysis

The data were analyzed using correlation and regression analysis.

Results

The invasive hemodynamic and Doppler aortic blood flow data at control state and during vasodilator therapy are summarized in table 1. Figure 3 demon-
strates an aortic blood flow velocity recording before and during administration of i.v. nitroprusside (case 14).

**Doppler Peak Flow Velocity**

Absolute values of Doppler PFV and invasive SVR at control periods and during peak effect of therapy in 18 interventions correlated \( r = -0.38 \) and were described by the regression equation: \( PFV = -1.93 \text{ SVR} + 73.43 \). Percent changes in SVR and PFV during vasodilator therapy were compared and are plotted in figure 4 \( (r = -0.89) \). Percent change in SVR showed a 21–45% change after therapy in nine of 18 studies. In all nine studies, PFV changed 17–57%. In the other nine studies, in which a 2–20% change in SVR was noted, the change in PFV did not exceed 13%.

The correlation between PFV and SV revealed an \( r \) value of 0.33 \( (PFV = 0.34 \text{ SV} + 2.87) \). Better correlation was demonstrated between the percent changes of SV and PFV with \( r = 0.75 \) (fig. 5).

**Doppler Ejection Time**

The correlation between the absolute values and percent change of ejection time (ET) and SVR revealed an \( r \) value of 0.01 and \(-0.15\), respectively. The data were described by the regression equation: \( ET = 0.000001 \text{ SVR} + 0.225 \) and \( \%\Delta ET = -8.8 \%\Delta \text{SVR} + 1.17 \). Correction of ejection time by heart rate (ETI) revealed the following correlations with SVR: \( r = -0.29 \) for the absolute measurements and \(-0.18 \) for the percent changes \( (ETI = 0.00003 \text{ SVR} + 0.42 \) and \( \%\Delta ETI = -5.37 \%\Delta \text{SVR} - 0.98 \)).

The absolute values of ET and SV correlated with \( r = 0.56 \) \( (ET = 0.0012 \text{ SV} + 0.16) \). Correlation between the percent changes of these parameters showed an \( r \) value of 0.70 \( (\%\Delta ET = 0.38 \%\Delta \text{SV} - 4.83) \). ETI showed a worse correlation with SV \( (r = -0.05) \).

**Table 1. Hemodynamic and Aortic Blood Flow Data at Control State and After Vasodilator Therapy**

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Dose</th>
<th>SV (ml)</th>
<th>SVR (dyn-sec-cm⁻³)</th>
<th>PFV (cm/sec)</th>
<th>LVET (sec)</th>
<th>FVI (cm)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>C</td>
<td>D</td>
<td>C</td>
<td>D</td>
<td>C</td>
</tr>
<tr>
<td>1</td>
<td>Nitroprusside</td>
<td>167 mg/min</td>
<td>57</td>
<td>54</td>
<td>1304</td>
<td>1048</td>
<td>0.255</td>
</tr>
<tr>
<td>2</td>
<td>Hydralazine</td>
<td>100 mg</td>
<td>56</td>
<td>59</td>
<td>1214</td>
<td>1187</td>
<td>0.277</td>
</tr>
<tr>
<td>3</td>
<td>Hydralazine</td>
<td>100 mg</td>
<td>40</td>
<td>60</td>
<td>969</td>
<td>554</td>
<td>0.212</td>
</tr>
<tr>
<td>4</td>
<td>Isordil</td>
<td>40 mg</td>
<td>52</td>
<td>58</td>
<td>661</td>
<td>678</td>
<td>0.239</td>
</tr>
<tr>
<td>5</td>
<td>Nitroprusside</td>
<td>100 mg/min</td>
<td>51</td>
<td>64</td>
<td>1608</td>
<td>1052</td>
<td>0.255</td>
</tr>
<tr>
<td>6</td>
<td>Hydralazine</td>
<td>50 mg</td>
<td>50</td>
<td>62</td>
<td>1983</td>
<td>1221</td>
<td>0.255</td>
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<tr>
<td>7</td>
<td>Isordil</td>
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<td>103</td>
<td>81</td>
<td>944</td>
<td>1215</td>
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<tr>
<td>8</td>
<td>Isordil</td>
<td>20 mg</td>
<td>69</td>
<td>66</td>
<td>839</td>
<td>955</td>
<td>0.170</td>
</tr>
<tr>
<td>9</td>
<td>Hydralazine</td>
<td>150 mg</td>
<td>61</td>
<td>66</td>
<td>695</td>
<td>776</td>
<td>0.191</td>
</tr>
<tr>
<td>10</td>
<td>Isordil</td>
<td>100 mg</td>
<td>67</td>
<td>81</td>
<td>776</td>
<td>705</td>
<td>0.191</td>
</tr>
<tr>
<td>11</td>
<td>Nitroprusside</td>
<td>100 mg/min</td>
<td>34</td>
<td>35</td>
<td>1656</td>
<td>1725</td>
<td>0.202</td>
</tr>
<tr>
<td>12</td>
<td>Nitroprusside</td>
<td>100 mg/min</td>
<td>34</td>
<td>33</td>
<td>1146</td>
<td>1081</td>
<td>0.190</td>
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<tr>
<td>13</td>
<td>Hydralazine</td>
<td>100 mg/min</td>
<td>29</td>
<td>36</td>
<td>1893</td>
<td>1030</td>
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<tr>
<td>14</td>
<td>Nitroprusside</td>
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<td>89</td>
<td>1209</td>
<td>949</td>
<td>0.271</td>
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<tr>
<td>15</td>
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<td>54</td>
<td>1756</td>
<td>978</td>
<td>0.202</td>
</tr>
<tr>
<td>17</td>
<td>NTGO 250</td>
<td>2 inches</td>
<td>25</td>
<td>45</td>
<td>1246</td>
<td>978</td>
<td>0.138</td>
</tr>
<tr>
<td>18</td>
<td>Hydralazine</td>
<td>100 mg</td>
<td>49</td>
<td>66</td>
<td>1248</td>
<td>1103</td>
<td>0.202</td>
</tr>
</tbody>
</table>

**Abbreviations:** C = control; D = vasodilator therapy; SV = stroke volume; SVR = systemic vascular resistance; PFV = peak flow velocity; LVET = left ventricular ejection time; FVI = flow velocity integral; NTGO = nitroglycerin ointment.
(ETI = -0.0001 SV + 0.32). The percent changes of these parameters showed an r value of 0.58 (%ΔETI = 0.16%ΔSV - 1.2).

**Doppler Flow Velocity Integral**

The correlation coefficient between the absolute values of Doppler aortic FVI and SVR was -0.31. The data were described by the regression equation: FVI = -2.81 SVR + 10.4. The relative changes of FVI and SVR showed an r value of -0.65 (fig. 6).

The relationship between the absolute values of FVI and SV for all 18 control and all 18 drug studies revealed an r value of 0.44 (FVI = 7.8 SV + 2.79). Higher correlation (r = 0.88) was found between the relative changes of these two measurements during therapy (fig. 7).

**Discussion**

Hemodynamic evaluation is desirable for the assessment of the effect of vasodilator therapy in patients with CHF. The available invasive technique, although reliable, is associated with some risk to the patient and is relatively expensive. A simple, noninvasive method to assess hemodynamic changes after therapeutic vasodilator therapy, therefore, would have an obvious clinical application. M-mode echocardiography has been successfully used to evaluate drug-induced changes in left ventricular size and function in normal subjects and in patients with cardiac diseases.7,8 However, the technique provides measurement of left ventricular dimensions that change only as a cube root of ventricular volumes changes and is of limited value in assessing the response to vasodilators in patients with...
CHF. Radionuclide studies provide an accurate assessment of left ventricular volumes and performance. However, this technique has a limited availability, is associated with a large capital outlay for instrumentation, and serial studies require repeated injections of radioactive material. Although the systolic time intervals have been used to evaluate therapeutic effect, the inherent limitations of this method in determining the functional status of the left ventricle has prevented widespread use.

Recent studies in dogs have shown a good correlation between changes in the aortic blood flow pattern as obtained by continuous-wave or pulsed Doppler ultrasound and SV as measured by the thermodilution or Fick methods. Buchtal et al. suggested the clinical value of Doppler measurements in the assessment of the cardiovascular response to drugs and fluid therapy in critically ill patients. The results of the present study support these preliminary findings by demonstrating that changes in Doppler aortic blood flow measurements are correlated with changes in SVR and SV after vasodilator therapy in patients with CHF.

Reduction of SVR in patients with heart failure improves the ability of the left ventricle to empty and, consequently, to shift the depressed ventricular function curve upward and to the left. This change is usually associated with an augmentation of ventricular ejection fraction. Our data show that a change in SVR is also associated with a change in peak aortic blood flow velocity, as manifested by an inverse correlation between percent changes of these two variables ($r = -0.89$).

The present study demonstrates that the magnitude of the change in peak aortic blood flow velocity allows a clear separation between patients who did and did not have a clinically important effect of therapy on the vascular resistance. The direction of change in SVR could be predicted in most of the cases by an opposite change in peak flow velocity. Two patients who did not follow this rule (nos. 9 and 12) showed only small changes in both SVR and PFV. This discrepancy probably reflects the error inherent in the accuracy and reproducibility of both techniques and demonstrates the problem of trying to assess small hemodynamic changes by Doppler velocimetry. Although SVR decreased in most cases who responded to therapy, a paradoxical marked increase in resistance was observed in one instance (study 7) and could be identified by its association with a large decrease in peak aortic flow velocity.

Despite the close relationship between the dynamics of SVR and PFV, a poor correlation ($r = 0.38$) was found between the absolute values of these variables. The aortic blood flow velocity, therefore, must be influenced by other factors, which probably include the state of myocardial contractility and the size and shape of both the aortic valve and the aorta. The volume of blood ejected by the left ventricle during each systole also does not seem to have an important effect on the absolute PFV as reflected by a correlation coefficient of only 0.33 between these variables.

Our study also demonstrates that a change in left ventricular ET does not correlate closely with a change in SVR. Percent changes in ET after vasodilator therapy correlated better with changes in SV, a finding in accordance with the results of Weissler and Schoenfeld, who assessed the correlation between changes in ET and SV in response to Cedilanid-D in patients with CHF. Our results did not demonstrate a close relationship between the absolute values of SV and the area under the flow velocity curve. This finding is not surprising; the measurement of aortic diameter is required for the assessment of volumetric blood flow using Doppler technique.

A change in SV is not necessarily associated with a predictable change in PFV or ET when evaluated separately. However, the effect on these two variables in combination, as reflected by changes in the area under the Doppler flow velocity curve (FVI), is indicative of
changes in SV in most patients in our study. Careful analysis of the individual data shows a small decrease in SV with no change in FVI in one case (case 8) and minimal increase in SV associated with a small decrease in FVI in another case (case 11). Thus, errors inherent in both techniques should limit the clinical usefulness of the Doppler technique in the assessment of small hemodynamic changes.

The correlation between changes in SV and changes in FVI is in agreement with data obtained in dogs by either manually positioning the Doppler transducer on the aortic arch or by the suprasternal approach. Our results are an extension of these experimental studies and demonstrate the clinical application of this technique for the noninvasive evaluation of acute hemodynamic changes in patients with CHF.

There are several potential sources of error in the measurement of the aortic flow velocity. One source of error can result from changes in the angle between the ultrasound beam and the long axis of the blood flow. By establishing the sample volume depth that produced the greatest blood flow velocity and by using the beat with the greatest obtainable maximum blood flow velocity for our analysis, this source of error was minimized.

Another potential source of error results from ambiguities that occur when one attempts to measure high flow velocities at long distances from the transducer. If the product of the distance from the transducer and the flow velocity exceeds the range velocity product of the instrument, accurate recording of peak flow velocity may not be reliable. We did not exceed the range velocity product of our instrument in any of our patients. However, this limitation of the pulsed Doppler technique should be considered when high-velocity flow is expected, such as during exercise. In addition to these potential sources of error, the presence of turbulent flow in situations such as aortic valve stenosis may preclude application of Doppler technique for the prediction of hemodynamic changes after therapy. This was not a problem in the present study because none of our patients showed turbulent aortic flow.

In conclusion, the results of this study demonstrate a close correlation between changes in aortic PFV as measured by Doppler velocimetry and acute changes in invasively measured SVR after vasodilator therapy. In addition, changes in the Doppler FVI, i.e., the area under the Doppler flow velocity curve, provide an accurate assessment of changes in SV during vasodilator treatment in patients with CHF. These findings suggest that aortic blood flow measurements by Doppler velocimetry are useful clinically for the noninvasive evaluation of acute drug therapy in patients with heart disease. Further studies are warranted to evaluate the potential application of the technique in the long-term assessment of vasodilator therapy in patients with CHF.

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Hemodynamic and Neuroendocrine Responses to Acute and Chronic Alpha-adrenergic Blockade with Prazosin and Phenoxybenzamine

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SUMMARY We investigated the relevance of the selective α1-adrenergic receptor blockade produced by prazosin to its blood pressure–lowering efficacy in man. The hemodynamic and neuroendocrine responses to the acute and chronic oral administration of prazosin and phenoxybenzamine were compared in a randomized, double-blind, placebo-controlled, crossover study of 11 patients with essential hypertension. These responses were also evaluated during lower body negative pressure and dynamic bicycle exercise, which produce potent but diversified activation of the sympathetic nervous system. In the acute studies, arterial blood pressure decreased to similar levels with prazosin or phenoxybenzamine; however, hemodynamic and neuroendocrine responses differed both before and during sympathetic nervous system activation. Prazosin lowered arterial blood pressure by reducing total peripheral resistance (p < 0.05). In contrast, phenoxybenzamine produced a modest reduction in cardiac output (8%, p < 0.05) with little change in total peripheral resistance, forearm vascular resistance or forearm blood flow. Additionally, plasma noradrenaline concentration and heart rate rose to significantly higher levels with prazosin (p < 0.02) than with phenoxybenzamine, a difference that was most evident with lower body negative pressure or dynamic exercise. Baroreceptor control of arterial pressure homeostasis was preserved with both agents, except during marked degrees of cardiovascular stress. With chronic therapy, the circulatory responses adapted to the α-adrenergic antagonists, and both drugs produced similar hemodynamic and neuroendocrine profiles. The differences with acute administration may be the result of a more rapid onset of action and a more marked degree of α-adrenergic blockade with prazosin than with phenoxybenzamine therapy, rather than to any difference in their α1- and α2-adrenergic receptor blocking properties. Moreover, the findings of the present study suggest that the prejunctional α2-receptor, autoinhibitory to sympathetic neuronal noradrenaline release, is of no functional significance in patients with essential hypertension.

SINCE their introduction in the 1950s,1-3 α-adrenergic antagonists have fallen into disrepute as therapeutic agents for the treatment of essential hypertension because of intolerable side effects such as tachycardia, postural hypotension and impotence and because of their weak antihypertensive effects.4 Prazosin, a recently developed α-adrenergic antagonist,5,6 is an effective antihypertensive agent that chronically produces little change in heart rate, cardiac output and renin release.7,8 The absence of reflexogenic effects with this agent may be explained by the finding in animal studies that prazosin blocks only α1-adrenergic receptors, which mediate vasoconstriction, and not α2-adrenergic receptors, which control stimulus-induced noradrenaline release from sympathetic nerve terminals.9-11 Thus, with prazosin, it has been postulated that prejunctional α2-receptor blockers remain functional and prevent the disproportionate increase in noradrenaline release, heart rate, cardiac output and renin release that counteract the antihypertensive effects of less selective antagonists, such as phenoxybenzamine and phentolamine.12 However, the hemodynamic and neuroendocrine effects of prazosin and those of conventional α-adrenergic antagonists have not been compared in man.

In the present study, the hemodynamic and neuroendocrine responses to the acute and chronic administration of prazosin and phenoxybenzamine were compared using a randomized, placebo-controlled, double-blind, crossover design. Although phentolamine blocks α2-adrenergic receptors more potently...
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